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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	20

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/921,004	ANDERSON ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- Th MAILING DATE of this communication app ars on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-19 and 25-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-19 and 25-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the claims

The Request for Continued Examination filed October 7, 2003 is acknowledged and has been entered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 3-19 and 25-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. On page 15, line 8 through page 18, line 5 in the specification. The applicant discloses abundant proteins within ranges and disclose the identification of markers of tissue damage that fall within a molecular weight range of 45kd. On page 5 of the specification the applicant discloses that the invention relates to a method of detecting and quantifying low molecular weight protein and/or peptide components in a biological sample, particularly in urine. The method comprises a number of steps that include, concentrating biological fluid; fractionating the concentrated material collected; separating the constituents of the fraction of interest and components of the original fluid. The applicant does not disclose the first fraction having substantially all proteins or peptides with a molecular weight greater than

about 3 kDa and below the filtration limits of a normal kidney found in the biological fluid. There is no description in the specification that substantially all proteins or peptides with a molecular weight greater than 3 kDa and below the filtration limits of a normal kidney found in the biological fluid are contained in the first fraction.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-19 and 25-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because the preamble of the claim does not correlate with the body of the claim. The preamble recites a method of detecting at least one low molecular weight protein and/or peptide component in a biological fluid. The body of the claim recites a first fraction having substantially all proteins or peptides and determining the proteins or peptides present in the first fraction. The body of the claim does not cover the situation were only one protein or peptide is determined.

Claim 1 is vague and indefinite because it is unclear if all the proteins or peptides present in the first fraction (i.e. greater than 3 kDa and below the filtration limits of a normal kidney, 55 kDa as defined on page 19 in the specification) are considered to be low molecular weight proteins. If so this contradict applicants definition provided in the specification on page 42 which discloses two fractions were generated at > and < 30 kDa. The proteins in the > 30 kDa fraction were considered as the high molecular

weight fraction, and the < 30 kDa fraction was considered as the low molecular weight fraction. Please clarify.

Claim 1, part (b) the recitation "substantially all" is vague and indefinite. It is unclear what is considered to be substantially all. There is no definition provided for the term in the specification. See deficiencies throughout the claims.

Claim 1, part (c) "greater than about 3kDa" is vague and indefinite. It is unclear what is considered to be greater than about. There is no description, definition or guidance provided for the term in the specification.

Claim 3, line 2 "other fluid" is vague and indefinite. It is unclear what applicant intends. Further, there is no definition or guidance provided for the term in the specification

Claim 7, line 1 "said concentrating step" there is insufficient antecedent basis for this limitation.

Claim 31, line 4 "capable of" is vague and indefinite. The recitation "capable of" is not a positive limitation and does not constitute a limitation in any patentable sense. See also deficiency found in claim 32.

Claim 36 the recitation "is not than urine" is vague and indefinite. It is unclear what applicant intends.

Claim 38 is vague and indefinite because it is unclear where in the process is the step of contacting a test biological fluid with said antibody against at least one of said proteins or peptides is occurring. Does it occur after step (a) or step (b) or step (c)?

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 1, 3, 5, 10 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Opiteck et al (Comprehensive Two-Dimensional high-Performance Liquid Chromatography for the Isolation of Overexpressed Proteins and Proteome Mapping, Analytical Biochemistry 258, 349-361, 1998).

Opiteck et al. disclose a method comprising size-exclusion chromatography which fractionates a sample containing proteins in a biological fluid by weight. Opiteck et al teaches that a fraction of the sample is further subjected to reversed-phase chromatography to separate similarly sized proteins in the fraction. Opiteck disclose that the fraction contains proteins that have a mass above 3 kDa and below the filtration limits of a normal kidney (Figs. 4, 5, 7 and Table 1). Opiteck et al disclose that the sample is recovered from the RPLC and interesting fractions are determined by mass spectrometry.

With respect to the recitation the first fraction having substantially all proteins or peptides with a molecular weight grater than about 3 kDa and below filtration limits of a normal kidney as recited in the instant claims. Opiteck teaches that the fractions contain proteins that fall within this range and since it is unclear what is meant by substantially all proteins in the instantly recited claims. It is the Examiner's position that

Opiteck reads on the instantly recited claims. Further, by way of applicant's own disclosure on page 19 in the specification, the normal filtration cutoff of the kidney is 55 kDa. Therefore, it is the Examiner's position that Opiteck reads on the instantly recited claims.

Further, it is noted that in the instantly recited claims that applicant appears to try and establish a cut-off range by including the limitation and below the filtration limits of a normal kidney. However, the instantly recited claims do not exclude proteins having a molecular weight above the filtration limits of a normal kidney being present in the first fraction.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 3-5, 8, 9, 12-14, 17, 25 and 29-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stevens (US 6,410,692) in view of Liu et al (5,492,834).

Stevens discloses a method for removing interfering macromolecules from a liquid sample. Stevens et al disclose applying the sample to an affinity matrix to remove the interfering macromolecules. Stevens disclose centrifuging the sample. Stevens disclose recovering the liquid and subjecting the liquid sample to 2-D gel electrophoresis. Stevens disclose that the use of this 2-D gel electrophoresis allows for a large number of low abundant proteins to be identified and quantitated (col 12).

Stevens differ from the instant invention in failing to teach fractionating proteins in the fluid by molecular weight to produce a fractionated protein or peptide sample and separating a first fraction from the fractionated protein sample.

Liu et al disclose applying a liquid sample to a size exclusion gel. Liu et al disclose that the size exclusion gels have a molecular weight exclusion of at least 6,000. Liu et al disclose recovering a fraction of the fractioned sample and subjecting the sample to further analysis. The use of such an exclusion gel provides methods for analyzing body fluid samples for certain analytes while eliminating the effects of the

presence of interfering components and provides for methods for analyzing patient urine samples for low concentrations of proteins indicative of certain disease states.

It would have been obvious to one of ordinary skill in the art to incorporate size exclusion gels as taught by Liu et al into the method of Stevens because Liu et al shows that the use of such an exclusion gel provides methods for analyzing body fluid samples for certain analytes while eliminating the effects of the presence of interfering components and provides for methods for analyzing patient samples for low concentrations of proteins indicative of certain disease states.

10. Claims 6 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stevens and Liu in view of Furst (US 5,926,387).

See above for teachings of Stevens and Liu et al.

Stevens and Liu et al differ from the instant invention in failing to teach zonal sedimentation centrifugation on density gradients.

Furst et al disclose a technique, which, involves layering a sample containing the components of interest onto the top of a liquid column, which is stabilized by a density-gradient of an inert solute. Furst et al disclose that this process is known as Rate-zonal sedimentation. Rate-zonal sedimentation is used to improve the efficiency of the fractionation by separating the particles according to size (col 1, lines 45-67).

It would have been obvious to one of ordinary skill in the art to incorporate rate-zonal sedimentation as taught by Furst et al into the modified method of Stevens because Furst et al shows that rate-zonal sedimentation improves the efficiency of the fraction by separating the particles according to size.

With respect to the stationary phases comprising different mesh sizes as recited in the instant claims, the mesh sizes can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. Further, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

11. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stevens and Liu et al in view of O'Donnell et al (US 5,998,216).

See above for teachings of Stevens and Liu et al.

Stevens and Liu et al differ from the instant invention in failing to teach the addition of at least one protease inhibitor to the body fluid upon collection.

O'Donnell et al disclose the addition of protease inhibitor to urine. O'Donnell et al disclose that the addition of protease inhibitors to urine provides for maintaining and preserving the integrity of proteins and polypeptides present in a body fluid sample obtained ex-vivo (abstract). O'Donnell et al also disclose that these protease inhibitors provide a powerful effect on cytokines individually and collectively in human urine

samples; and enhances markedly the stability and the preservation effect for the cytokines under a variety of different collection and environmental conditions (col 13, lines 1-56).

It would have been obvious to one of ordinary skill in the art to incorporate the use of a protease inhibitor such as taught by O'Donnell et al into the modified method of Stevens because O'Donnell et al shows the addition of protease inhibitors to urine provides for maintaining and preserving the integrity of proteins and polypeptides present in a body fluid sample obtained ex-vivo. O'Donnell et al also disclose that these protease inhibitors provide a powerful effect on cytokines individually and collectively in human urine samples; and enhances markedly the stability and the preservation effect for the cytokines under a variety of different collection and environmental conditions.

12. Claims 10, 11 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stevens and Liu et al in view of Opiteck et al (Two-Dimensional SEC/RPLC Coupled to Mass Spectrometry for the Analysis of Peptides, Anal. Chem. 1997, 69, 2283-2291).

See above for teachings of Stevens and Liu et al.

Stevens and Liu et al differ from the instant invention in failing to specifically teach fractionating said first fraction by elution from a reverse phase stationary phase and identifying proteins or peptides by mass spectrometry.

Opiteck et al disclose methods for fractionating, separating, recovering and determining peptides. Opiteck et al disclose further fractionating a fraction by reversed phase liquid chromatography, which utilizes nonporous C-18 modified silica particles,

which produce fast and efficient analyses. Opiteck also disclose identifying the peptide by mass spectrometry. Opiteck disclose that the use of RPLC and mass spectrometry provided for fast and efficient analyses of protein samples.

It would have been obvious to one of ordinary skill in the art to incorporate reversed phase liquid chromatography and mass spectrometry into the method of Stevens because Opiteck shows that the use of RPLC and mass spectrometry provided for fast and efficient analyses of protein samples.

13. Claims 15, 16 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stevens and Liu et al in view of Hage et al (affinity Chromatography: A review of Clinical Applications, clinical Chemistry 45:5 593-615, 1999).

See above for teachings of Stevens and Liu et al.

Stevens and Liu et al differ from the instant invention in failing to teach further fraction from an affinity column.

Hage et al disclose methods comprising biological-like interactions for the separation and specific analysis of sample components. Hage et al disclose immunoaffinity columns and non-immunological affinity columns such as protein G and protein A. Hage et al disclose that affinity chromatography is rapidly becoming the separation method of choice in clinical laboratories and other biologically related fields such as pharmaceutical science and biotechnology. Hage et al disclose that affinity chromatography is an attractive alternative to traditional methods for the selective quantification and study of clinical samples and provides for the creation of an affinity system for almost any compound of clinical interest.

It would have been obvious to one of ordinary skill in the art to incorporate affinity chromatography as taught by Hage et al into the modified method of Stevens because Hage et al shows that affinity chromatography is an attractive alternative to traditional methods for the selective quantification and study of clinical samples and provides for the creation of an affinity system for almost any compound of clinical interest.

Response to Arguments

14. Applicant's arguments with respect to claim1, 3-19 and 25-38 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Van Eyk et al. (US 2002/0072590) teach methods for separating a mixture of proteins in a biological sample and methods for detecting and profiling proteins in biological samples.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (703) 305-1444. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gary Counts
Examiner
Art Unit 1641
December 8, 2003

LONG V. LE
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11/10/03